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Applicant: Bjeldanes et al.

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Docket No. B03-074-1

Examiner: Betton, Timothy E

Title: *3,3'-Diindolylmethane Antiandrogenic Compositions*

DECLARATION UNDER 37CFR1.132

I, Leonard F. Bjeldanes, declare and state as follows:

1. I am a Professor of Toxicology at the University of California, Berkeley. I have a Ph.D. in Organic Chemistry from the University of California, Los Angeles. My area of research is the study of the efficacy and mode of action of naturally occurring cancer protective agents in food. I have authored numerous publications on the anticarcinogenic effects of indole-3-carbinol and its *in vivo* derivative 3,3'-diindolylmethane. I am an inventor of the subject application.

2. The claimed method is applied to a host determined to be in need of an antiandrogen. The Specification teaches that DIM is an antiandrogen, and shows that DIM operates similar to other androgen receptor antagonists like Casodex (e.g. Specification, p.16, line 25 – p.17, line 25). Those skilled in the art are in the business of diagnosing and treating people in need of antiandrogens, and the Specification teaches and exemplifies suitable such hosts (e.g. Specification, p.4, lines 9-29; Examples II & III).

Androgen-dependent pathologies and antiandrogenic treatments are well-known in the art, as are diagnostic methods for determining whether a patient is in need of such treatments or is subject or predisposed to such pathologies.

In my opinion, the Specification reasonably conveys possession of the invention as claimed to those skilled in the art.

3. Claim 1 recites a two-step method for providing an antiandrogen to a host determined to be in need thereof.

The method is applied to a host determined to be in need of an antiandrogen. The Specification teaches that DIM is an antiandrogen, and shows that DIM operates similar to other androgen receptor antagonists like Casodex (e.g. Specification, p.16, line 25 – p.17, line 25). Those skilled in the art are in the business of diagnosing and treating people in need of antiandrogens, and the Specification teaches and exemplifies suitable such hosts (e.g. Specification, p.4, lines 9-29; Examples II & III).

The first step is simply contacting the host with an effective amount of an antiandrogenic, optionally substituted DIM. The Specification teaches and exemplifies how to prepare and administer the subject compositions (e.g. Specification, p.7, line 11 – p.9, line 7; Examples II and III). Effective amounts of the compositions are readily determined empirically (e.g. Specification, p.9, lines 4-7.

The second step is simply detecting a resultant antiandrogenic response in the host. The Specification teaches that DIM is an antiandrogen, and shows that DIM operates similar to other androgen receptor antagonists like Casodex (e.g. Specification, p.16, line 25 – p.17, line 25). Those skilled in the art are in the business of diagnosing and treating people in need of antiandrogens, and the Specification teaches and exemplifies suitable such hosts (e.g. Specification, p.4, lines 9-29; Examples II & III). In addition, the Specification teaches and exemplifies a wide variety of clinically relevant and validated animal models for antiandrogen activity (e.g. Specification, p.5, lines 13-16).

In my opinion, one of ordinary skill in the art would be able to practice the claimed invention without undue experimentation.

4. What constitutes a "reduction" in a pathology or progress of the pathology, as the term is used in claim 3, is self-evident to one skilled in the art.

In my opinion, the claims are sufficiently clear such that one of ordinary skill in the art to which the invention pertains would understand the metes and bounds of the claims and be on notice as to what is the scope of the claims.

5. Our claims recite a two-step method for providing an antiandrogen to a host determined to be in need thereof: 1) contacting the host with an effective amount of an antiandrogenic, optionally substituted 3-3'-diindolylmethane (DIM); and 2) detecting a resultant antiandrogenic

response in the host. These claims are expressly limited to targeting a host determined to be in need of antiandrogen therapy.

The claims of U.S. Pat. No. 6,001,868 do not teach or suggest the subject claims; they do not teach or suggest that treating with DIM a host determined to be in need of antiandrogen therapy.

In my opinion, the present invention, at the time it was made, would not have been obvious to one of ordinary skill in the art at the time the invention was made over the claims of the cited patent.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful, false statements may jeopardize the validity of the application and any patent issuing therefrom.

Date: 1/3/07

Leonard F. Bjeldanes

Leonard F. Bjeldanes, Ph.D.

Clinical Trials (PDQ®)

Patient Version **Health Professional Version** **Last Modified:** 9/27/2006 **First Published:** 3/17/2006

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Phase I Study of Absorption-Enhanced Diindolylmethane (BioResponse-DIM®) in Patients With Nonmetastatic, Hormone-Refractory Prostate Cancer and Rising Prostate-Specific Antigen Levels

Alternate Title
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Alternate Title

Diindolylmethane in Treating Patients With Nonmetastatic Prostate Cancer That Has Not Responded To Previous Hormone Therapy

Basic Trial Information

Phase	Type	Status	Age	Sponsor	Protocol IDs
Phase I	Treatment	Active	18 and over	NCI	**WSU-D-2979** WSU-0507002581, NCT00305747

Objectives

Primary

1. Establish the maximum tolerated dose, dose-limiting toxicity, and a recommended phase II dose of absorption-enhanced diindolylmethane (BioResponse-DIM® [BR-DIM]) in patients with nonmetastatic, hormone-refractory prostate cancer and rising serum prostate-specific antigen (PSA) levels.
2. Evaluate the toxicities of BR-DIM.

Secondary

1. Evaluate the plasma pharmacokinetics of twice daily oral administration of BR-DIM in this patient population.
2. Evaluate the effect of BR-DIM supplementation on serum PSA level.
3. Correlate changes in expression levels of lymphocytes NF-kB with serum PSA levels in patients

taking BR-DIM supplementation.
4. Determine quality of life measures in patients taking BR-DIM supplementation.

Entry Criteria

Disease Characteristics:

- Histologically proven adenocarcinoma of the prostate
- Prostate specific antigen (PSA)-only failure after local therapy (surgery, radiation therapy, brachytherapy, or cryotherapy)
- Rising PSA despite androgen-deprivation therapy with castrate levels of testosterone (< 50 ng/dL)
  - Two successive rising PSA levels at least 1 week apart
  - PSA ≥ 5 ng/mL
- Patients with a history of combined hormonal therapy must continue luteinizing-hormone releasing-hormone agonist treatment but must demonstrate rising PSA after anti-androgen withdrawal
- No evidence of distant metastasis by bone scan and CT scan
- No known brain metastases requiring active therapy

Prior/Concurrent Therapy:

- See Disease Characteristics
- At least 28 days since prior radiotherapy
- At least 28 days since prior investigational agents for treatment of prostate cancer
- At least 4 weeks since prior flutamide
- At least 6 weeks since prior bicalutamide
- No other concurrent antineoplastic agents
- No concurrent warfarin-related anticoagulants
- No concurrent proton-pump inhibitor drugs for gastroesophageal reflux disease (e.g., rabeprazole, esomeprazole magnesium, lansoprazole, omeprazole, or pantoprazole sodium)
- No concurrent micronutrient supplements or dietary soy products
  - One daily multivitamin allowed

Patient Characteristics:

- ECOG performance status ≤ 3
- Life expectancy ≥ 12 weeks
- Absolute neutrophil count ≥ 1,500/mm^3
- Platelet count ≥ 100,000/mm^3
- Hemoglobin ≥ 8.0 g/dL
- Total bilirubin ≤ 1.5 times upper limit of normal (ULN)
- SGOT and/or SGPT ≤ 2.5 times ULN AND alkaline phosphatase normal OR alkaline phosphatase ≤ 4 times ULN AND SGOT and/or SGPT normal
- Creatinine clearance ≥ 60 mL/min OR creatinine normal
- Fertile patients must use effective contraception
- None of the following conditions within the past 6 months:
  - Myocardial infarction
  - Severe or unstable angina
  - Symptomatic congestive heart failure
  - Cerebrovascular accident or transient ischemic attack
  - Coronary/peripheral artery bypass grafting
- No other severe acute or chronic medical or psychiatric condition or laboratory abnormality that would preclude study participation

Expected Enrollment

A total of 20 patients will be accrued for this study.

Outcomes

Primary Outcome(s)

Maximum tolerated dose during study and for 30 days after
Dose limiting toxicity during study and for 30 days after
Toxicity during study and for 30 days after

Secondary Outcome(s)

Plasma pharmacokinetics as measured by occurrences of toxicity at baseline, 20, 60, 120, 180, 240, and 480 minutes
Serum prostate specific antigen as measured by complete plasma concentration-time profile at baseline, day 1 of each course, and at study termination
Correlate changes in expression levels of NF-kB lymphocytes in with serum prostate specific antigen levels by serum prostate specific antigen level at baseline, second course, and study termination
Quality of life (QOL) by Life Orient. Test-Rev., Duke-UNC Func. Social Support Questionnaire, EORTC QOL questionnaire, QLQ-PR25 questionnaire, and the Hosp. Anxiety & Depression Scale at baseline, day 1 of each course, and study termination

Outline

This is an open-label, dose-escalation study.

Patients receive oral absorption-enhanced absorption-enhanced diindolylmethane (BioResponse-DIM® [BR-DIM]) twice daily on days 1-28. Treatment repeats every 28 days for up to 12 courses in the absence of disease progression or unacceptable toxicity.

Cohorts of 3-6 patients receive escalating doses of BR-DIM until the maximum tolerated dose (MTD) is determined. The MTD is defined as the dose preceding that at which 2 of 6 patients experience dose-limiting toxicity. At least 6 patients are treated at the MTD.

Quality of life is assessed at baseline, on day 1 of each course, and at the completion of study therapy.

Trial Contact Information

Trial Lead Organizations

Barbara Ann Karmanos Cancer Institute

Elisabeth Heath, MD, Protocol chair	Ph: 313-576-8715; 800-527-6266 Email: heathe@karmanos.org

Trial Sites

U.S.A.

Michigan

Detroit

Barbara Ann Karmanos Cancer Institute

Clinical Trials Office - Barbara Ann Karmanos Cancer Institute	Ph: 800-527-6266

Registry Information

Official Title	Phase I Study of Bioresponse-dim® in Non-Metastatic, Hormone-Refractory Prostate Cancer Patients with Rising Serum PSA
Trial Start Date	2005-08-24
Registered in ClinicalTrials.gov	NCT00305747
Date Submitted to PDQ	2005-12-05
Information Last Verified	2006-11-05
NCI Grant/Contract Number	CA22453

Note: The purpose of most clinical trials listed in this database is to test new cancer treatments, or new methods of diagnosing, screening, or preventing cancer. Because all potentially harmful side effects are not known before a trial is conducted, dose and schedule modifications may be required for participants if they develop side effects from the treatment or test. The therapy or test described in this clinical trial is intended for use by clinical oncologists in carefully structured settings, and may not prove to be more effective than standard treatment. A responsible investigator associated with this clinical trial should be consulted before using this protocol.

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